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Pharmacovigilance: need and future prospective in herbal and ayurvedic medicines

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ABSTRACT

Pharmacovigilance is related to the protection of public health and monitoring of adverse drug reaction. Herbal and ayurvedic medicines make up an important module towards alternative medicine. It is becoming ever more popular in today's world as people seek out for natural remedies. Herbal and ayurvedic medicines are generally considered as safe but they also need consistent monitoring for adverse effects. To compete with the growing pharmaceutical market, there is an exigency to develop and scientifically validated more medicinally useful herbal products. This review article provides an overview of the need of the pharmacovigilance for herbal and ayurvedic medicines and future aspects of pharmacovigilance in herbal drugs.

Keywords: Pharmacovigilance, adverse drug reaction, herbal drugs, ayurveda.

1. Introduction

Pharmacovigilance is the science dedicated to reduce the risk of drug-related harms to the consumers. Pharmacovigilance refers to the process of identifying side effects of drugs, their treatment, documentation, reporting and regulatory decisions based on these findings. The worldwide movement for the improvement of patient safety is gaining momentum so the subject of drug safety becomes even more prominent in the present day scenario. In India also, pharmacovigilance practice is gaining pace in keeping with time.

WHO define the Pharmacovigilance (PV) as the pharmacological science relating to the detection, evaluation, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines [1].

It is widely accepted that a drug has to go through various phases of clinical trial to establish its safety and efficacy before it is marketed commercially. However, the clinical trials offer various limitations, like; strict criteria of inclusion and exclusion make it to be used in a very selective group of patients; special population groups like children, pregnant woman, and old age population are not studied during the trials; and other factors causing drug reactions such as genetic factors, environmental factors, and drug-drug interactions may not have been studied during the clinical trials [2]. Hence, need of pharmacovigilance has been demanded, which include the detection, assessment, and prevention of adverse drug reactions in humans [3-4].

In a vast country like India with a population of over 1.2 Billion with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines, different socioeconomic status, it is important to have a standardized and robust pharmacovigilance and drug safety monitoring programme for the nation. Collecting this information in a systematic manner and analyzing the data to reach a meaningful conclusion on the continued use of these medicines is the rationale to institute this program for India. Since, there are considerable social and economic consequences of ADRs there is a need to engage health-care professionals, in a well-structured programme to build synergies for monitoring ADRs. The purpose of the Pharmacovigilance Program of India is to collect, collate and analyze data to arrive at an inference to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public [5].

The important aspects of pharmacovigilance includes :Improve patient care and safety in relation to the use of medicines and all medical and Para medical interventions [6]; Research the efficacy of drug and by monitoring the adverse effects of drugs; keeping track of drastic effects

of drugs; contributing to the assessment of benefit, harm, effectiveness and risk of medicines encouraging their safe and effective use; Promoting education and clinical training in pharmacovigilance and its effective communication to the public.

2. Indian Scenario

The Central Drugs Standard Control Organization (CDSCO) has initiated a country-wide Pharmacovigilance programme under the aegis of DGHS, Ministry of Health & Family Welfare Government of India. The National Pharmacovigilance Centre shall coordinate the program at CDSCO. The National Centre will operate under the supervision of the National Pharmacovigilance Advisory Committee to recommend procedures and guidelines for regulatory services. [7] However, the national pharmacovigilance system has been known to exhibit various functions which include, promoting pharmacovigilance in the country in order to collect and manage adverse drug reaction; reporting of medication errors and suspected substandard drugs; collaborating and harmonizing with existing adverse reaction collection activities within the country; identifying signals of medicine safety; undertaking assessment of risk and options for risk management; identifying the possible quality problems in medicines resulting in adverse reactions; supporting the identification of medicine quality issues; providing effective communication on aspects related to medicine safety; applying resulting information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines; developing and maintaining drug utilization information; and identifying issues associated with unregulated prescribing and dispensing of medicines [8-10].

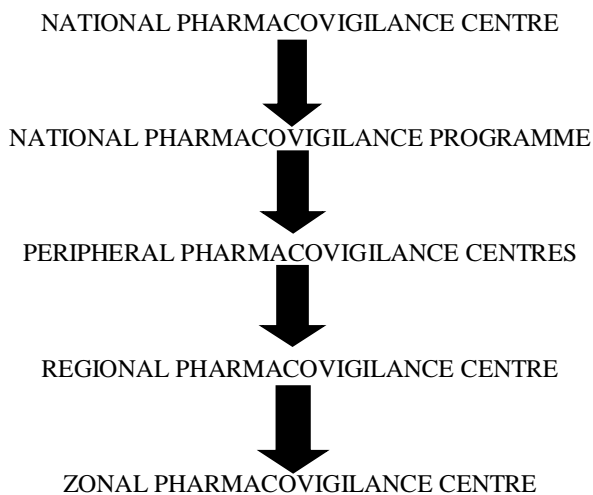


Fig 1: Flow chart of the flow of information/ different level of centre involved

3. Organizations Involved

The National Pharmacovigilance Advisory Committee (Npac)

Oversee the performance of various Zonal, Regional and Peripheral Pharmacovigilance centers as well as recommend possible regulatory measures based on the data received from various centers. It also oversees data collection and assessment, interpretation of data as well as publication of

ADR monitoring data. The Committee also periodically evaluates their protocol compliance levels to ensure that the data received is homogenous and can be scientifically pooled for informed regulatory decisions. Wherever necessary, NPAC also seeks the opinion of experts in various specializations. The Drugs Controller General of India (DCGI) is the member secretary of the committee. The National Pharmacovigilance Advisory Committee (NPAC) is to play this role until a formal set up to monitor the entire programme is in place with the Central Drugs Standard Control Organisation.

4. The Central Drugs Standard Control Organization Headquarters

The Central Drugs Standard Control Organization (CDSCO) is the national regulatory body for Indian pharmaceuticals and medical devices, and serves parallel function to the European Medicines Agency of the European Union, the PMDA of Japan and the Food and Drug Administration of the United States. Within the CDSCO, the Drug Controller General of India (DCGI) regulates pharmaceutical and medical devices. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC). It is divided into zonal offices which do pre-licensing and post-licensing inspections, post-market surveillance, and recalls when needed [11].

5. Indian Pharmacopoeia Commission

Indian Pharmacopoeia Commission (IPC) is an Autonomous Institution of the Ministry of Health and Family Welfare, Govt. of India. IPC is created to set standards of drugs in the country. It's basic function is to update regularly the standards of drugs commonly required for treatment of diseases prevailing in this region. It publishes official documents for improving Quality of Medicines by way of adding new and updating existing monographs in the form of Indian Pharmacopoeia (IP). It further promotes rational use of generic medicines by publishing National Formulary of India. IPC also acts as a National Coordination Centre for Pharmacovigilance Programme of India, thereby coordinating all the activities related to pharmacovigilance in India [11].

6. WHO Collaborating Centre for International Drug Monitoring: The Uppsala Monitoring Centre

The World Health Organization (WHO) is a specialized agency of the United Nations (UN) that is concerned with international public health. The Uppsala Monitoring Centre (UMC) is an independent foundation and a centre for international service and scientific research. The operational responsibility for the ADR monitoring programme rests with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, (UMC), in Sweden. The system started with 10 countries that had already established national systems for spontaneous adverse reaction reporting and who agreed to contribute data. For an effective international system to become operative, a common reporting form was developed, agreed guidelines for entering information formulated, common terminologies and classifications prepared and compatible systems for transmitting, storing and retrieving and disseminating data were created. The ADRs database in Uppsala currently contains over eight million reports of suspected ADRs [11].

7. National Institute of Biologicals

National Institute of Biologicals (NIB), an autonomous Institution under the Ministry of Health & Family Welfare (MOHFW)-Government of India is a premier Scientific Organization and a Centre of Excellence to ensure quality of biologicals and vaccines in the country. The institute responsibly assures and reviews the quality of number of biological products available through domestic manufacturers or imports. The operations are carried out in the state of the art Facility of the Institute and in close coordination with Government of India regulatory authorities as Office of Drug Controller of India, Indian Pharmacopoeia's Commission.

Indian Pharmacopoeia Commission in collaboration with National Institute of Biologicals has launched a Haemovigilance programme across the country under its Pharmacovigilance Programme of India (PvPI) with following Terms of References:

1. To track Adverse Reactions/ Events and incidence associated with Biologicals, Blood transfusion and Blood product administration (Haemovigilance) as well as tissue organ and cell therapy transplantation.
2. To help identify trends, recommend best practices and interventions required to improve patient care and safety, while reducing overall cost of the healthcare system^[11].

8. Pharmacovigilance in Respect to Ayurvedic and Herbal Medicine

Herbal medicine

Herbal medicines consist of plant or its part to treat injuries, disease or illnesses and are used to prevent and treat diseases and ailments or to promote health and healing. It is a drug or preparation made from a plant or plants and used for any of such purposes. Herbal medicines are the oldest form of health care known to mankind^[12-14]. World Health Organization (WHO) has defined herbal medicines as finished, labeled medicinal products that contain active ingredients, aerial or underground parts of the plant or other plant material or combinations. World Health Organization has set specific guidelines for the assessment of the safety, efficacy, and quality of herbal medicines. WHO estimates that approx 81% of the world populations presently use herbal medicine for primary health care^[15].

9. Adverse Drug Reaction of Herbal Medicines

An adverse reaction (ADR) is defined as a noxious and unintended response to a marketed health product, which occurs at doses normally used or tested for the diagnosis, treatment, or prevention of a disease or the modification of an organic function^[16]. It is undeniable that plants have an important role in the development of modern medicines. More than 60 to 70% of modern medicines in the world market are directly or indirectly derived from plant products.

Widely reported issues such as adverse drug reactions associated with Ephedra and Aristolochia have shown that herbal medicinal products can produce toxicity in human beings. The most common adverse effects reported are hepatic and renal problems. However, it is difficult to identify the causative agent associated with the ADRs encountered because traditional herbal preparations often contain multiple ingredients. The WHO database has over sixteen thousand suspected herbal case reports. Due to the

lack of clinical trials for most herbal medicinal products, post marketing pharmacovigilance becomes a critical source of safety information. However, the assessment of adverse reactions associated with herbal medicinal products offers unique challenges in the quantity and quality of available information^[17-18].

10. Drug Interactions

Mostly patients taking drugs with a narrow therapeutic index like Cyclosporine, Digoxin, Phenytoin, Procainamide, Theophylline, Warfarin etc. should be discouraged from using herbal products^[19]. All drugs with narrow therapeutic index may either have increased adverse effects or be less effective when used in conjunction with herbal products. Ginkgo is used for Alzheimer's disease and causes increased bleeding with aspirin. Ginseng has multiple uses and causing synergism with monoamine oxidase inhibitors. Kava is used as anxiolytic and shows synergism with benzodiazepines. St. John's Wort is used as antidepressant and causes reduced plasma levels of warfarin, cyclosporine, oral contraceptives, theophylline etc^[20].

11. Ayurveda

Ayurveda, the knowledge of life, immortalized in the form of elegant Sanskrit stanzas in the samhitas describe diagnosis and therapy of disease as well as ways to maintain positive health^[21, 22]. The major goals of pharmacovigilance, namely to improve patient care and safety in relation to drug use, and thus promote rational drug use are recurrent themes of ayurvedic pharmacology (dravyaguna vigyan) and therapeutics (chikitsa)^[23]. The use of ayurvedic medicines is popular in India - and in recent times has become accepted in other countries. Associated with this increasing use, are growing concerns about the safety of ayurvedic medicines^[24, 25].

There is a popular misconception that ayurvedic medicines are devoid of adverse reactions. However, the Charaka Samhita, which is a classic text book of ayurveda, describes all the adverse reactions to medicines when they are prepared or used inappropriately. Charaka also describes, elegantly, several host-related factors to be considered when selecting medicines in order to minimize adverse reactions like the constitution of the patient (prakriti), age (vayam), disease (vikruti), tolerance (previous exposure) (satmya), psychological state (satwa), digestive capacity (ahara-shakti), capacity for exercise (vyayama shakti), quality of tissues (Sara), physical proportions of the body (sahanan) and strength (bala)^[26].

Interestingly, classical ayurveda prescribes metals and minerals as medicines given as bhasmas (incinerated mineral formulations) or in combination with plants as herbo-mineral formulations (e.g. Arogyavardhini). Manufacturing procedures for these medicines are stringent, and adverse reactions are described when precautions are not taken while manufacturing and administering these medicines^[27]. Although these medicines are widely used in India, doubts about their long-term safety come up due to the presence of toxic metals in them^[28] and there are reports related to adverse reactions^[29].

12. Challenges in implementation of pharmacovigilance in Ayurveda

The various challenges in proper implementation of pharmacovigilance in ayurveda includes: very low reporting

of ADR; ignorance among physicians regarding ADR; false belief that ayurveda drugs have no expiry date, though this factor has been taken care of by introducing a rule regarding shelf life of all forms of drugs in Drugs and Cosmetics Act, 1945 [30]; Lack of quality assurance and control in manufacture of ayurvedic medicine, which act as a confounding factor in diagnosing the adverse reaction.

13. Pharmacovigilance of Herbal and Ayurvedic Medicines

The purpose of pharmacovigilance is to detect, assess, understand and to prevent the adverse effects or any other possible drug-related problems, related to herbal, traditionally and complementary medicines [31]. Herbal medicines are widely used in both developed and developing countries however, in recent years, there are several high-profile herbal safety concerns having an impact on the public health. Herbal medicines are traditionally considered as harmless but as medicinal products they require drug surveillance in order to identify their risks.

Various methods in pharmacovigilance are passive surveillance includes spontaneous reporting and stimulated reporting, active surveillance by sentinel sites, drug event monitoring, registries, comparative observational studies by survey study, case control study, targeted clinical investigations by investigate drug-drug interactions and food- drug interactions [32]. The importance of genetic factors in determining an individual susceptibility to adverse drug reactions is well documented and this implies to herbal medicines as well as to conventional drugs. Pharmacovigilance is therefore one of the important post-marketing safety tools in ensuring the safety of pharmaceutical and related health products [33].

14. Role of the Pharmacist Practitioner in Pharmacovigilance

“Safety monitoring of medicines in common use should be an integral part of clinical practice. The degree, to which clinicians are informed about the principles of pharmacovigilance, and practice according to them, has a large impact on healthcare quality. Education and training of health professionals in drug safety, exchange of information between national centres, the coordination of such exchange, and linking clinical experience of drug safety with research and health policy, all serve to enhance effective patient care. National programmes for pharmacovigilance are perfectly placed for identifying research necessary for better understanding and treatment of drug-induced diseases.” An important clinical responsibility of the pharmacist is in the early detection of ADRs and other drug-related problems as well as monitoring the effectiveness of medicines. The pharmacist, as a part of the healthcare team, is a source of both information and critical evaluation of drug information. The pharmacist’s expertise is vital to the application of the safety profile of a medicine to the needs of a particular patient. [34]

15. Recommendations

Based on these observations, there are several ways we can move forward in attempting to embrace pharmacovigilance systems into herbal and ayurveda:

- Introduce pharmacovigilance concepts into the curriculum at the under-graduate and post-graduate

level.

- Encourage studies on drug safety.
- Create awareness about the science of pharmacovigilance among physicians, patients and paramedical staff.
- Development and validation of scales to assess the causality of the reported reactions to herbal and ayurvedic medicines.
- Human resource development is a key feature for the success of this enterprise. It will be necessary to train experts in the science of Pharmacovigilance and include them not only in reporting but also assessment of the adverse reactions.

The need of the hour is to educate the physicians and encourage them to analyse and report any adverse effect that occurs in a patient. The industry should take concrete steps to generate confidence and reliability for its products. [35]

16. Conclusion

Medicinal herbs as potential source of therapeutics aids has attained a significant role in health care system all over the world for human beings not only in the diseased condition but also as potential material for maintaining proper health [36]. It is clear that the herbal industry can make great strides in the world. With the increased use of herbal products, the future worldwide labeling practice should adequately address quality aspects. Standardization of methods and quality control data on safety and efficacy are required for understanding of the use of herbal medicines [37]. A major factor impeding the development of the medicinal plant based industries in developing countries has been the lack of information on the social and economic benefits that could be derived from the industrial utilization of medicinal plants. [38] The monitoring the safety of herbal medicinal products, in the market or in the pipeline, will definitely go a long way in restoring the confidence of their safety.

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